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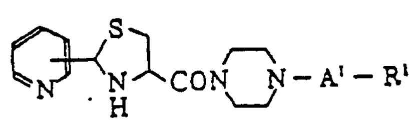
(54) Pyridylthiazolidine carboxamide derivatives and their intermediates and production of both.

(57) This invention provides pyridylthiazolidine carboxamide derivatives shown by general formula (I) and pharmaceutically acceptable salts thereof:



wherein A^1 is a single bond, carbonyl group or lower alkylene group which may include a carbonyl group and R^1 is a heterocyclic ring which may be substituted with a lower alkyl group; it further provides N-substituted piperazine derivatives useful as intermediates for preparing said compounds (I). Compounds (I) and their salts have PAF-antagonistic activity.

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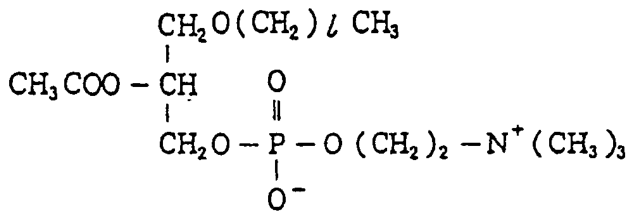
PYRIDYLTHIAZOLIDINE CARBOXAMIDE DERIVATIVES AND THEIR INTERMEDIATES AND PRODUCTION OF BOTH

This invention relates to novel pyridylthiazolidine carboxamide derivatives and salts thereof which have platelet activating factor (PAF) antagonizing activity and further relates to their intermediates.

PAF is a chemical substance released from human and other animal cells and is an acetylglyceryl ether of phosphorylcholine as represented by the following formula:

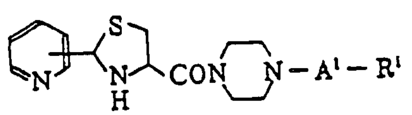


wherein ℓ is the integer 15 or 17.

PAF is physiologically active and causes contraction of the airway smooth muscle, increased vascular permeation, platelet aggregation and blood pressure fall and the like. It is thought to be a factor inducing asthma, inflammation, thrombosis, shock and other symptoms. Therefore, studies of substances capable of antagonizing the physiological activities of PAF are under way and several anti-PAF agents have been reported (e.g. European patent application No. 178,261 (A), U.S. patent Nos. 4,539,332, 4,656,190 and 4,621,038, European patent No. 115,979 (B) and British patent application No. 2,162,062 (A)).

We have found that novel pyridylthiazolidine carboxamide derivatives differing in chemical structure from the known anti-PAF agents have excellent anti-PAF activity and that novel N-substituted piperazine derivatives are useful as intermediates for preparing the pyridylthiazolidine carboxamide derivatives aforementioned.

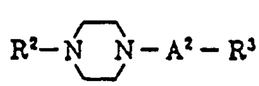
The pyridylthiazolidine carboxamide derivatives of the present invention are of formula (I) :



(I)

wherein A^1 represents a single bond, a carbonyl group or a lower alkylene group which may contain a carbonyl group and R^1 represents a heterocyclic group which may be substituted by lower alkyl.

Further , the N-substituted piperazine derivatives useful as the intermediates are of formula (II):



(II)

wherein A^2 represents a lower alkylene group which may contain a carbonyl group; R^2 represents a hydrogen atom or an amino-protecting group and R^3 represents a heterocyclic group (except a pyridyl group) which may be substituted with lower alkyl.

Herein the term "lower" means, unless othewise specified, a straight or branched carbon chain containing 1 to 6 carbon atoms.

Accordingly, the "lower alkyl group" specifically includes, among others, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl etc.

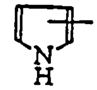
The "lower alkylene group which may contain a carbonyl group" represented by A^1 or A^2 means "lower

alkylene group" and "lower alkylene group which contains a carbonyl group". The "lower alkylene group" is a straight or branched alkylene group having 1 to 6 carbon atoms and specifically includes methylene, ethylene, trimethylene, methylmethylene, propylene, tetramethylene, 1-methyltrimethylene, 2-methyltrimethylene, 3-methyltrimethylene, ethylethylene, 1,2-dimethylethylene, 1,1-dimethylethylene, 2,2-dimethylethylene, propylmethylene, pentamethylene, 1-methyltetramethylene, 2-methyltetramethylene, 3-methyltetramethylene, 4-methyltetramethylene, 1,1-dimethyltrimethylene, 1,2-dimethyltrimethylene, 2,2-dimethyltrimethylene, 2,3-dimethyltrimethylene, 1,3-dimethyltrimethylene, 3,3-dimethyltrimethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 3-ethyltrimethylene, 1,1,2-trimethylethylene, 1,2,2-trimethylethylene, 1-ethyl-1-methylethylene, 1-ethyl-2-methylethylene, 2-ethyl-1-methylethylene, 2-ethyl-2-methylethylene, 1-propylethylene, 2-propylethylene, butylmethylene, hexamethylene, 1-methylpentamethylene, 2-methylpentamethylene, 3-methylpentamethylene, 4-methylpentamethylene, 5-methylpentamethylene and the like.

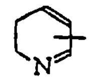
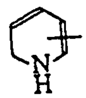
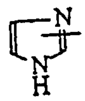
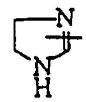
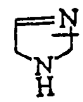
The "lower alkylene group which contains a carbonyl group" is a straight or branched oxoalkylene group and specifically includes 2-oxoethylene ($-CH_2CO-$), 1-oxoethylene ($-COCH_2-$), 3-oxotrimethylene ($-CH_2CH_2CO-$), 2-oxotrimethylene ($-CH_2COCH_2-$), 1-oxotrimethylene ($-COCH_2CH_2-$), 1-methyl-2-oxoethylene ($-CH(CH_3)CO-$), 2-methyl-1-oxoethylene ($-COCH(CH_3)-$), 4-oxotetramethylene ($-CH_2CH_2CH_2CO)-$, 3-oxotetramethylene ($-CH_2CH_2COCH_2-$), 2-oxotetramethylene ($-CH_2COCH_2CH_2-$), 1-oxotetramethylene ($-COCH_2CH_2CH_2-$), 1-methyl-3-oxotrimethylene ($-CH(CH_3)CH_2CO-$), 2-methyl-3-oxotrimethylene ($-CH_2CH(CH_3)CO-$), 1,1-dimethyl-2-oxoethylene ($-C(CH_3)_2CO-$), 1-ethyl-2-oxoethylene ($-CH(C_2H_5)CO-$), 3-methyl-1-oxotrimethylene ($-COCH_2CH(CH_3)-$), 2-methyl-1-oxotrimethylene ($-COCH(CH_3)CH_2-$), 2,2-dimethyl-1-oxoethylene ($-COC(CH_3)_2-$), 2-ethyl-1-oxoethylene ($-COCH(C_2H_5)-$), 5-oxopentamethylene($-CH_2CH_2CH_2CH_2CO-$), 1-oxopentamethylene ($-COCH_2CH_2CH_2CH_2-$), 6-oxohexamethylene ($-CH_2CH_2CH_2CH_2CH_2CO-$), 1-oxohexamethylene ($-COCH_2CH_2CH_2CH_2CH_2-$) and the like.

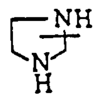
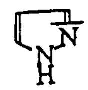
The "heterocyclic group" R^1 is a saturated or unsaturated, heteromono- or heteropolycyclic ring with 1 to 3 heteroatoms selected from oxygen, sulfur and nitrogen atoms; among others, a 5- or 6-membered heteromonocyclic group with 1 to 3 heteroatoms is preferable. R^3 may be the same as R^1, with the exception of pyridyl.

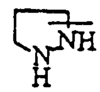
Accordingly, preferable heterocyclic groups are, for example, 1 to 3 nitrogen atom-containing saturated or unsaturated, 5- or 6-membered heteromonocyclic groups such as

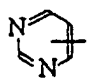
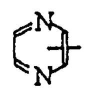
pyrrolyl (),

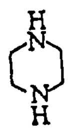
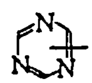
pyrrolinyl (), pyrrolidinyl (),

pyridyl (), dihydropyridyl ( ,  ,  , ), piperidinyl (), imidazolyl (), imidazolinyl ( , ),

imidazolidinyl (), pyrazolyl (),

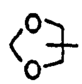
pyrazolinyl (), pyrazolidinyl (),

pyrimidinyl (), pyrazinyl (),

piperazinyl () and triazinyl ();

1 or 2 oxygen atom-containing saturated or unsaturated, 5- or 6-membered heteromonocyclic groups such as

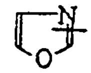
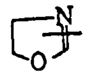
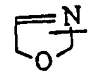
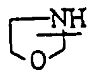
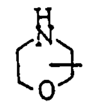
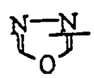
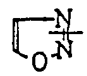
furyl (), tetrahydrofuryl (),

pyranyl ( , ), tetrahydropyranyl () and dioxolyl ();

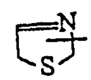
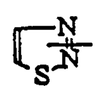
sulfur atom-containing saturated or unsaturated, heteromonocyclic groups such as

thienyl () and tetrahydrothienyl ();

oxygen and nitrogen atom-containing saturated or unsaturated, heteromonocyclic groups such as

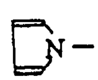
oxazolyl (), oxazolinyl ( , ), oxazolidinyl (), isooxazolyl (), isooxazolinyl (), morpholinyl () and oxadiazolyl ( ,  , );

and sulfur and nitrogen atom-containing saturated or unsaturated, heteromonocyclic groups such as

thiazolyl (), thiazolinyl ( , ), thiazolidinyl (), isothiazolyl (), isothiazolinyl (), isothiazolidinyl (), thiomorpholinyl (), thiadiazolyl ( ,  , )

and the like. These groups may be substituted with a lower alkyl group afore-mentioned.

When a pyrrolyl group binds at the ring nitrogen atom, it is shown by

 ;

the other heterocyclic groups herein having at least one non-tertiary ring nitrogen atom may take the corresponding form.

Examples of the amino-protecting group R^2 are specifically urethane type protective groups such as benzyloxycarbonyl type protective groups (for example benzyloxycarbonyl (carbobenzoxy), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl and 3,4,5-trimethoxybenzyloxycarbonyl groups) and alkyloxycarbonyl type protective groups (for example tert-butoxycarbonyl, tert-amyloxycarbonyl, p-biphenyl isopropyloxycarbonyl, diisopropylmethyloxycarbonyl and adamantyloxycarbonyl groups); acyl type protective group such as formyl, trifluoroacetyl, phthalyl, tosyl (toluenesulfonyloxy), o-nitrophenylsulfenyl, p-methoxy-o-nitrophenylsulfenyl, benzoyl, chloroacetyl and acetoacetyl groups; alkyl type protective groups such as trityl, benzhydryl, benzyl and trimethylsilyl groups; and allylidene type

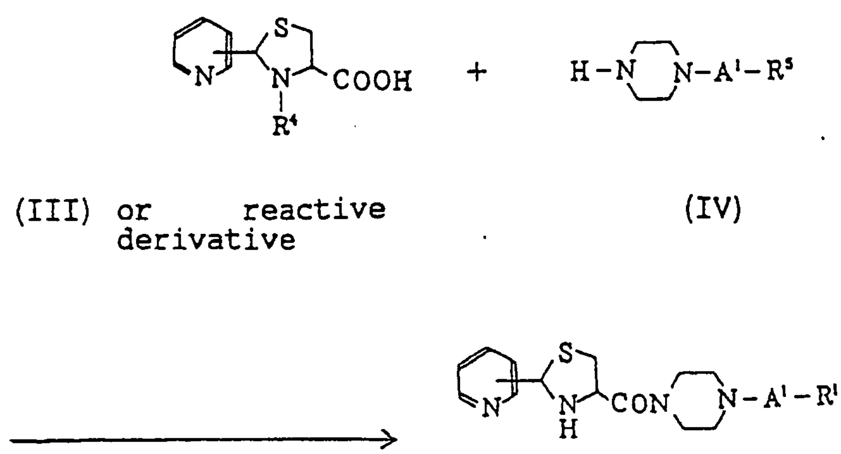
protective groups such as benzylidene and 2-hydroxyallylidene groups.

The compounds (I) can form salts, which are within the invention. Such salts include addition salts with inorganic acids such as hydrochloric, sulfuric, nitric, phosphoric , hydrobromic and hydroiodic acids and with organic acids such as acetic, oxalic, succinic, citric, maleic, malic, fumaric, tartaric, picric, methanesulfonic and ethanesulfonic acids; salts with acidic amino acids such as glutamic and aspartic acids; and quaternary ammonium salts from quaternarization with alkyl halides such as methyl chloride, bromide and iodide.

The compounds (I) have at least two asymmetric carbon atoms and the isomers that can thus exist, both in individual separate form and in any mixture of two or more, fall within the invention.

The compounds (I) can be produced by various synthetic methods taking advantage of the characteristics of the skeletal structure and various substituents. Typical examples of applicable production processes are given below.

Process 1 (Amidation A)



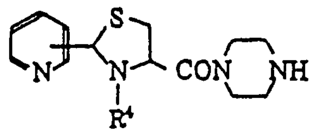
(III) or reactive derivative

(IV)

Deprotection as necessary

(I)

Process 2 (Amidation B)



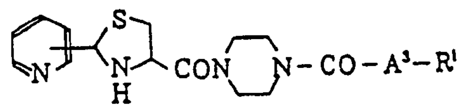
+ R^5-A^3-COOH

(V)

(VI) or reactive derivative

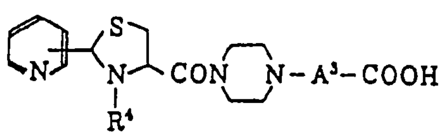
$\longrightarrow$

Deprotection as necessary

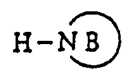


(Ia)

Process 3 (Amidation C)



+

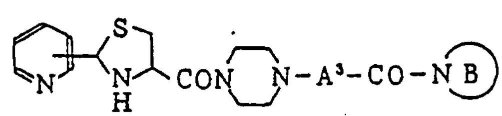


(VII) or reactive derivative

(VIII)

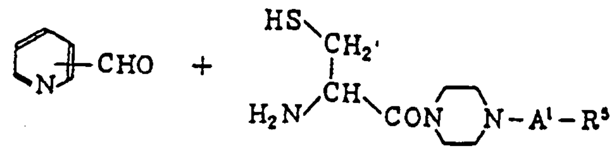
$\longrightarrow$

Deprotection as necessary

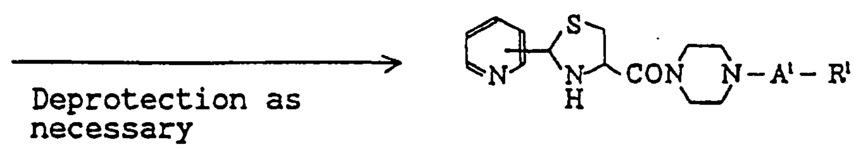


(Ib)

Process 4 (Cyclization)

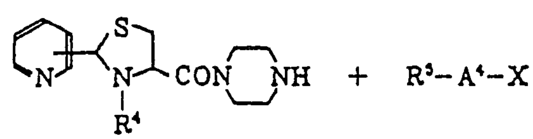


(IX) (X)

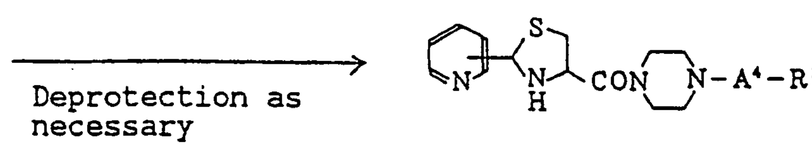


(Ic)

Process 5 (N-Alkylation A)

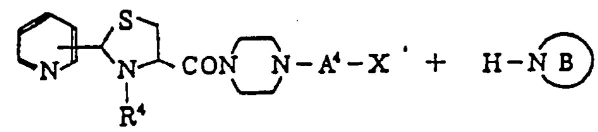


(XI) (XII)

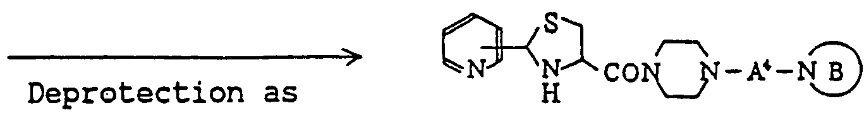


(Id)

Process 6 (N-Alkylation B)



(XIII) (XIV)



Deprotection as necessary

(Ie)

In the above reaction formula , A^1 and R^1 are defined as above and the other substituents are defined as follows:

R^4: a hydrogen atom or an amino-protecting group;

R^5: the same group as R^1 which may have an amino-protecting group;

A^3: a single bond or a lower alkylene group;

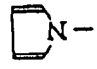
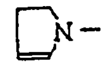
 :

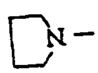
a heterocyclic group containing one or more non-tertiary nitrogen atoms;

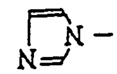
X: a halogen atom or an organic sulfonic acid residue; and

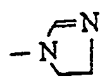
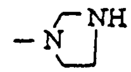
A^4: the same group as A^1 where the X-end is not a carbonyl group.

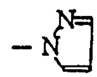
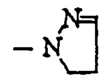
For amino-protecting group R^4, there may be mentioned the same groups as for amino-protecting group R^2. For the lower alkylene group A^3 may be mentioned the A^1 lower alkylene groups that have 1 to 5 carbon atoms. The R^4 heterocyclic groups are those among R^1 which have at least one ring nitrogen atom which is not tertiary, and preferably include

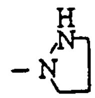
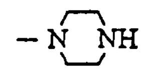
pyrrolyl (), pyrrolinyl (),

pyrrolidinyl (), dihydropyridyl (),

piperidinyl (), imidazolyl (),

imidazolinyl (), imidazolidinyl (),

pyrazolyl (), pyrazolinyl (),

pyrazolidinyl (), piperadinyl () and

and the like.

Examples of halogen atom X are an iodine, bromine, chlorine atom, etc.; examples of the organic sulfonic acid residue include lower alkylsulfonyloxy groups such as methanesulfonyloxy, ethanesulfonyloxy, etc. and aromatic sulfonyloxy groups such as benzenesulfonyloxy, toluene (especially p-toluene)sulfonyloxy, etc.

The production processes are described in more detail hereinbelow.

Process 1

Compound (I) can be produced by reacting thiazolidine carboxylic acid (III) or reactive derivative thereof with 4-substituted piperazine (IV) or salt thereof.

As reactive derivatives of compound (III), there may be mentioned acid halides such as acid chlorides or bromides; acid azides; active esters with N-hydroxybenzotriazole or N-hydroxysuccinimide; symmetric acid anhydrides; mixed acid anhydrides with alkylcarbonic acids or p-toluenesulfonic acid and the like.

When compound (III) is reacted in the free carboxylic acid form, it is advantageous to carry out the reaction in the presence of a condensing agent such as dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole.

The reaction conditions may vary to some extent depending on the starting compound, particularly on the kind of reactive derivative of compound (III). Generally, however, it is advantageous to carry out the reaction in an organic solvent inert to the reaction, such as pyridine, tetrahydrofuran, dioxane, ether, N,N-dimethylformamide, benzene, toluene, xylene, methylene chloride, dichloroethane, chloroform, ethyl acetate, acetonitrile or the like, using the starting compounds of (III) and (IV) in equimolar amounts or one of them in excess.

According to the kind of reactive derivative, or when the starting compound (IV) is used in salt form, it is in some instances advatageous to carry out the reaction in the presence of a base, for example, an organic base such as trimethylamine, triethylamine, pyridine, picoline, lutidine, dimethylaniline or N-methylmorpholine or an inorganic base such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide or potassium hydroxide. It is also possible to promote the reaction by using the starting compound (IV) in excess. Pyridine may be also used as a solvent.

The reaction temperature may vary, hence should suitably be selected, depending on the kind of said reactive derivative.

It is favorable in this reaction to use starting compounds where R^4 is not a hydrogen atom and R^5 is not a secondary ring amino group

$(>\mathrm{NH}).$

It is possible, however, to use the compounds having such groups by means of protective group introduction prior to reaction and deprotection after reaction.

The deprotection, performed as necessary, can be carried out in conventional manner. For instance, a protective group such as benzyloxycarbonyl, benzyl, substituted benzyl, trityl, benzhydryl group, etc. is easily removed by catalytic reduction; a group such as tert-butoxycarbonyl, benzyloxycarbonyl group, etc. by treatment with acids such as hydrobromic acid/acetic acid, hydrobromic acid/trifruoroacetic acid, trifluoroacetic acid, hydrochloric acid/acetic acid, hydrochloric acid/dioxane, etc.; and a trimethylsilyl group by contacting with water.

Process 2

Compound (Ia) where A^1 is -CO-A^3- can be produced by reacting piperazinamide compound (V) with carboxylic acid (VI) or reactive derivative thereof and then carrying out deprotection as necessary.

The reaction conditions and so forth of this process are substantially the same as in Process 1.

Process 3

Compound (Ib) can be produced in substantially the same manner as in Process 1 using a carboxylic acid (VII) or reactive derivative thereof and cyclic amine (VIII).

Process 4

Compound (Ic) can be produced by reacting carbonyl compound (IX) with β-mercaptoamine (X).

The reaction is carried out in a solvent of alcohol such as methanol, ethanol, isopropanol, etc. or aqueous alcohol, using the compounds (IX) and (X) in about equimolar amounts or one of them in excess, generally at room temperature.

Deprotection can be substantially the same as in Process 1.

Process 5

Compound (Id) can be produced by reacting compound (XI) with compound (XII), followed by deprotecting as necessary.

When using halide compounds as the starting compound (XII), it is advantageous to carry out the reaction in an organic solvent such as N,N-dimethylformamide, dimethylsulfoxide, aceton, methylethylketone (2-butanone), methanol, ethanol, methylenechloride, ethylenechloride, chloroform, ether, tetrahydrofuran, dioxane, etc., or water or in a mixed solvent, using the starting compounds (XI) and (XII) in about equimolar amounts or one of them in slight excess at room temperature, under heating or refluxing.

For smooth reaction, it is some instances advantageous to add a di- or tert-organic base such as pyridine, picoline, N,N-dimethylaniline, N-methylmorpholine, trimethylamine, triethylamine, dimethylamine, etc. or an inorganic base such as potassium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium hydroxide, etc.

When using compounds with an organic sulfonic acid residue as the starting compound (XII), it is advantageous to perform the reaction in the same solvent as in the process using the halide compounds afore-mentioned, using the starting compounds (XI) and (XII) in equimolar amounts or one of them in slight excess and under cooling or at room temperature.

The reaction time may be suitably selected taking various kinds of the reaction conditions into account. Deprotection of the amino group is as in Process 1.

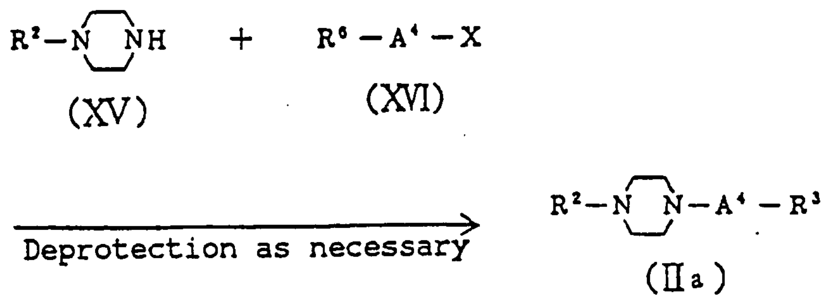
Process 6

Compound (Ie) can be produced by reacting compound (XIII) with a compound (XIV), followed by deprotecting the amino group if necessary.

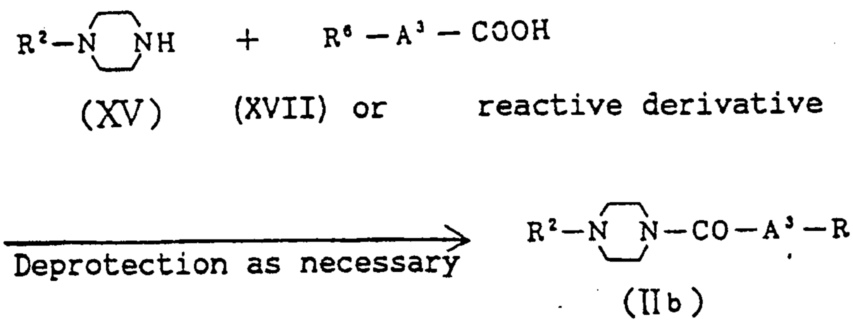
The reaction can be carried out as in Process 5.

The above intermediates (II) can be produced by various synthetic processes. Typical Examples of applicable processes are described in detail below.

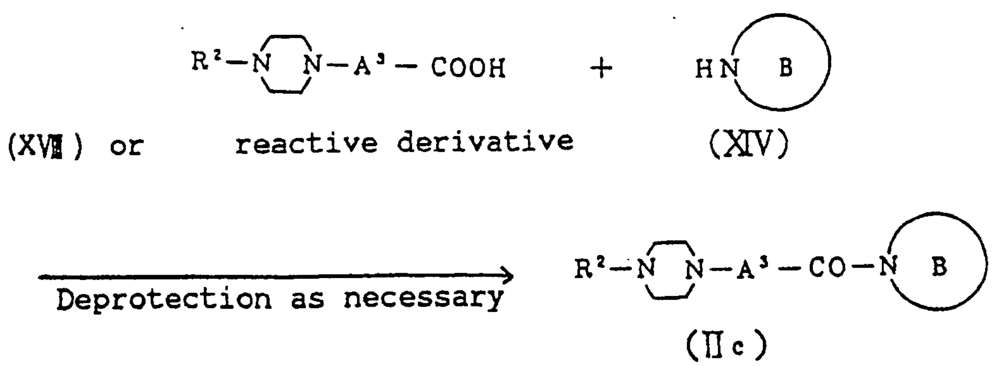
Process (a)



Process (b)



Process (c)



In the above formulae, R^2, R^3, A^3, A^4 and

are defined as above, and R^6 represents R^3 which may have an amino-protecting group. As examples of the amino-protecting group, there may be mentioned the same groups as for R^2.

Process (a)

Intermediate compound (IIa) can be produced by reacting piperazine (XV) with halide or sulfonate compound.

The reaction can be carried out as in Process 5.

When an amino-protecting group is employed in both R^2 and R^6, it is advantageous to select the same protective group and to deprotect simultaneously in one step. Deprotection may, of course, be carried out stepwise if protective groups of different reactivity are used.

Process (b)

Intermediate (IIb) can be produced by reacting compound (XV) with carboxylic acid (XVII) or its reactive derivative.

In respect of kinds of reactive derivative of the compound (XVII) and reaction conditions, the process is substantially the same as in Process 2. Also, the different protective groups may be employed as in Process (a).

Process (c)

Intermediate (IIc) can be produced by amidating compound (XVIII) or its reactive derivative with compound (XIV).

The reaction is the same as in Process (b).

The resultant compounds (I) and intermediates (II) of the present invention are isolated in the free form or in the form of salts thereof and purified. The salts, as necessary, may be prepared by subjecting the free-form compounds to a conventional salt formation reaction.

Isolation and purification can be performed by applying ordinary procedures , such as extraction, concentration, crystallization, filtration, recrystallization and various forms of chromatography.

As already mentioned, the compounds (I) may occur as isomers such as racemic compounds, optically active isomers and diastereomers either singly or in mixtures. Stereochemically pure isomers may be prepared by using appropriate starting compounds or by using a general method of optical resolution [e.g. the method which comprises conversion to diastereomer salts with an optically active acid in general use (e.g. tartaric acid)]. Separation of diastereomer mixtures can be realized in conventional manner, for example by fractional crystallization or chromatography.

The compounds (I) and salts thereof according to the invention have PAF-antagonizing activity and are useful in the treatment and prevention of various diseases caused by PAF. In particular, they can be used as antiasthmatics, antiinflammatory agents, antiulcer agents, shock symptom alleviating agents, therapeutic agents for ischemic heart diseases, liver diseases, thrombosis and nephritis, rejection inhibitors for use in organ transplantation, etc.

Some of the compounds of the invention have vasodilating activity and such compounds are useful as vasodilators as well.

The anti-PAF activity of the compounds according to the invention has been confirmed by the following test:

EFFECT ON PLATELET ACTIVATING FACTOR (PAF)-INDUCED PLATELET AGGREGATION IN PLASMA

Method:

Nine volumes of blood were drawn from the central ear artery of male rabbit (Japan white, 3 kg) directly into plastic syringe containing 1 volume of 3.8 % sodium citrate. The blood was centrifuged at 270×g for 10 minutes and the platelet rich plasma (PRP) was removed. The pellet was further centrifuged at 1,100×g for 15 minutes. The supernatant was used as platelet poor plasma (PPP). PRP was adjusted to 5×10^5 cells/μℓ with PPP. PAF-induced platelet aggregation was measured by the method of G.V.R. Born and M.J. Cross [Journal of Physiology, 168, 178-195 (1963)]. That is, the change of light transmission in PAF (10^{-8})-induced PRP was measured using NBS HEMA TRACER (Nikou Bio Science, Japan). The test compound was added two minutes before addition of PAF. Percent inhibition with the compound was calculated by dividing the percent aggregation in the presence of the compound by that in the control, and then the IC_{50} values were calculated. The compounds of Examples 6 and 5 were potent inhibitors having IC_{50} values of 1.0×10^{-7} and 2.5×10^{-7} M, respectively. These compounds did not inhibit the platlet aggregation induced by ADP (3 μM), arachidonic acid (100 μM) or collagen (10 μg/ml), and hence the results suggest that the compounds of this invention are specific antagonists of PAF.

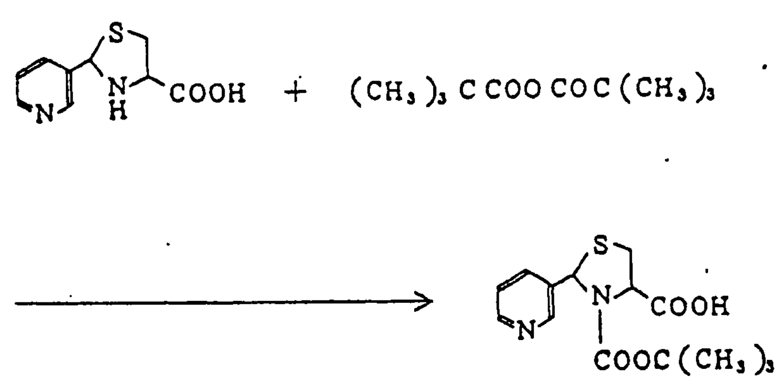
The compound (I) or its non-toxic salt of the present invention can be orally or parenterally administered as it is or as a medical composition with a pharmaceutically acceptable carrier or excipient (e.g., tablets, capsules, powders, granules, pills, ointments, syrups, injections, inhalants, suppositories, etc.). The dose depends on the patients to be treated, administration route, symptoms, etc., but is usually 0.1 to 500 mg, preferably 1 to 200 mg,per adult per day and is orally or parenterally administered in 2 or 3 sub-doses per day.

The compounds (II) are useful intermediates for production of compounds (I); compound (II) , after deprotection if it has a protective group or as it is if it has no protective group, may be subjected to the reaction of Process 1.

The following examples are further illustrative of the present invention.

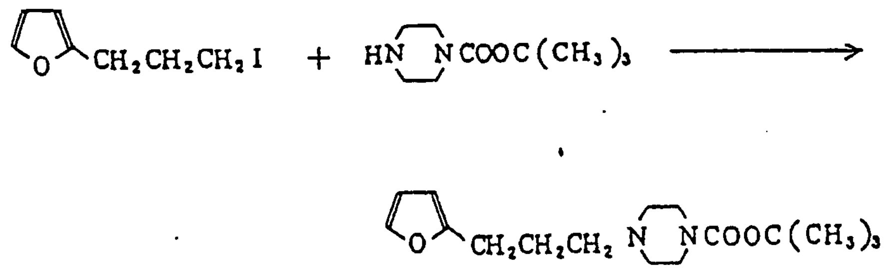
In the following, NMR indicates a nuclear magnetic resonance spectrum with TMS as an internal standard and MS indicates mass spectrum.

Reference Example 1



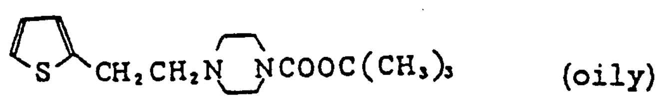
Di-tert-butyl dicarbonate (2.4g) and 10 ml of 1 N aqueous sodium hydroxide were added to a mixture of 2.1 g of 2-(3-pyridyl)thiazolidine-4-carboxylic acid, 20 ml of water and 40 ml of dioxane at a temperature not higher than 4° C, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, 30 ml of water was added, the pH was adjusted to 2 to 3 by addition of 0.5 M aqueous citric acid, and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate to give 1 g of N-tert-butoxycarbonyl-2-(3-pyridyl)thiazolidine-4-carboxylic acid. Melting point 167° C - 169° C.

Intermediate Example 1



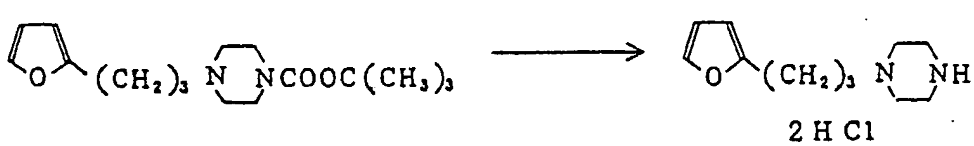
To a mixture of 1.16 g of 1-tert-butoxycarbonylpiperazine, 1.47 g of 2-(3-iodopropyl)furan and 20 ml of N,N-dimethylformamide was added 0.86 g of anhydrous potassium carbonate, and the mixture was stirred overnight at room temperature. To the reaction solution was added 300 ml of ethyl acetate, the solution was washed successively with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography and eluted with ethyl acetate to give 1.5 g of oily 1-tert-butoxycarbonyl-4-[3-(2-furyl)propyl]piperazine.
NMR ($CDCl_3$)
δ : 1.44(9H, s), 1.7 - 2.0(2H, m), 2.2 - 2.5 (6H, m), 2.66(2H, t), 3.3 - 3.6(4H, m), 5.9 - 6.1(1H, m), 6.2 - 6.4(1H, m), 7.2 - 7.4(2H, m)
MS : m/z 294 (M^+)

Intermediate Example 2



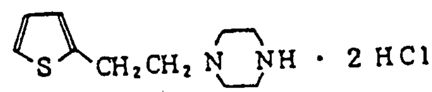
1-tert-butoxycarbonyl-4-[2-(2-thienyl)ethyl]piperazine was prepared in the same manner as in Intermediate Example 1.
NMR ($CDCl_3$)
δ : 1.48(9H, s), 2.3 - 2.8(6H, m), 2.8 - 3.2 (2H, m), 3.3 - 3.6(4H, m), 6.8 - 7.4(3H, m),
MS : m/z 296 (M^+)

Intermediate Example 3



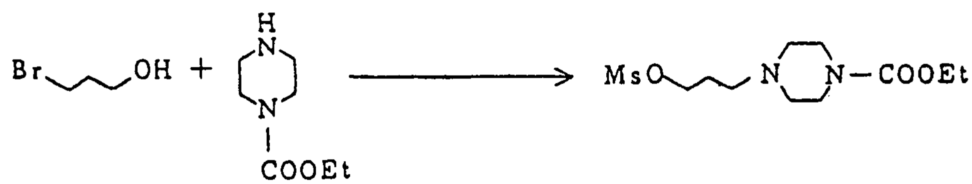
To 1.5 g of 1-t-butoxycarbonyl-4-[3-(2-furyl)propyl]-piperazine was added 5 ml of trifluoroacetic acid under ice-cooling, and the resultant mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure, and then dissolved in ethyl acetate (10 ml). To the solution was added 4 N hydrochloric acid-dioxane solution under ice-cooling to yield 1.3 g of 1-[3-(2-furyl)-propyl]piperazine• 2 hydrochloride.
NMR (DMSO - d_6)
δ : 1.7 - 2.4(2H, m), 2.5 - 2.9(2H, m), 3.0 - 3.8 (10H, m), 6.0 - 6.5(2H, m), 7.5 - 7.8(2H, m),
MS : m/z 184 (M^+ - 2HCl)

Intermediate Example 4



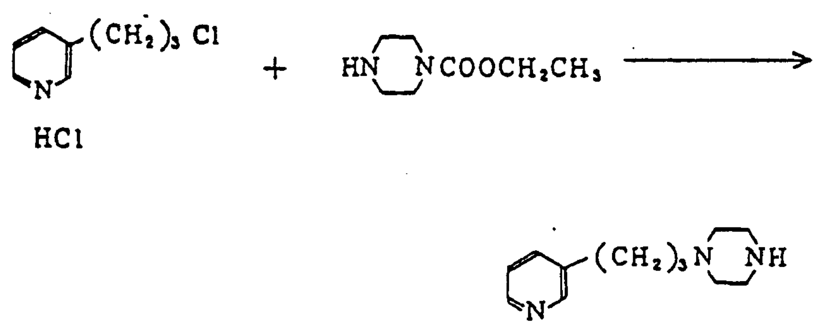
1-[2-(2-thienyl)ethyl]piperazine• 2 hydrochloride was obtained in the same manner as in Intermediate Example 3.
NMR (DMSO - d_6)
δ : 3.2 - 3.8(12H, m), 7.0(2H, d), 7.3 - 7.8(2H, m),
MS : m/z 197 (M+1 - 2HCl)

Intermediate Example 5



To a solution of 3-bromopropanol (4.17 g), ethyl 1-piperazinecarboxylate (4.74 g)and 2-butanone (20 ml) was added anhydrous potassium carbonate (4.74 g), followed by refluxing for 5 hours. After cooling, the reaction mixture was diluted with ethyl acetate (100 ml) and water (50 ml). The organic layer was taken using a separating funnel and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The resultant residue was dissolved in dichloromethane (150 ml). To the solution were added 4-dimethylaminopyridine (6.21 g) and methanesulfonylchloride (2.0 ml) and the mixture stirred under ice-cooling for 3 hours. After adding water(50 ml) to the reaction mixture, the organic layer was separated and after drying the solvent was distilled off under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: 2 % methanol-ethyl acetate) to yield 4.76 g of 1-ethoxycarbonyl-4-(3-mesyloxypropyl)piperazine.
NMR ($CDCl_3$)
δ : 1.26(3H, t), 1.68 - 2.20(2H, m), 2.25 - 2.70 (6H, m), 3.02(3H, s), 3.34 - 3.68(4H, m), 3.92 - 4.50(4H, m)

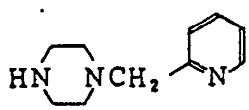
Intermediate Example 6



A mixed solution of 3-(3-chloropropyl)pyridine (1.92 g),ethyl 1-piperazinecarboxylate (1.6 g), anhydrous potassium carbonate (3.0 g),potassium iodide (1 g), tetra-n-butylammonium bromide (0.1 g)and 2-butanon (50 ml) was refluxed for 24 hours. To the reaction mixture was added water (50 ml),and the product was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried over

anhydrous magnesium sulfate and concentrated to dryness under reduced pressure to yield 1-ethoxycarbonyl-4-[3-(3-pyridyl)propyl]piperazine. This was dissolved in a mixture of 20 % sodium hydroxide (25 ml) and ethanol (25 ml) and the solution was refluxed for 2 days. The reaction mixture was concentrated under reduced pressure and to the residue was added ethyl acetate (100 ml) and anhydrous magnesium sulfate. After stirring the resultant mixture, the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure to yield 1.56 g of oily 1-[3-(3-pyridyl)propyl]piperazine.
NMR ($CDCl_3$)
δ : 1.6 - 2.0(2H, m), 2.2 - 2.5(6H, m), 2.66(2H, t), 7.1 - 7.3(1H, m), 7.4 - 7.6(1H, m), 8.3 - 8.6(2H, m)
MS : m/z 205 (M^+)

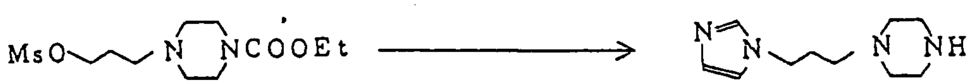
Intermediate Example 7



1-(2-pyridylmethyl)piperazine

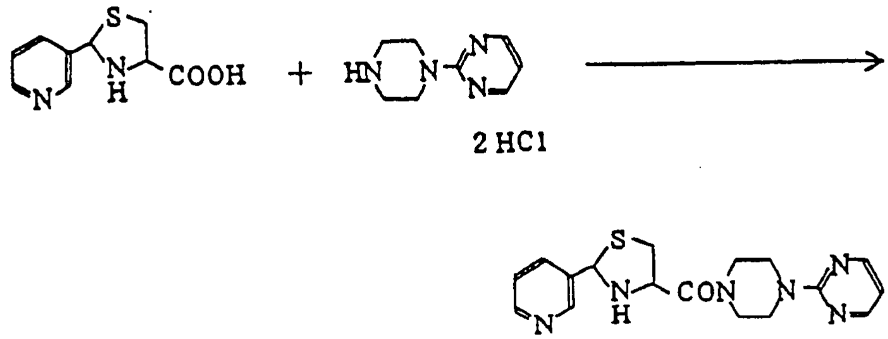
The compound of Intermediate Example 7 was obtained in the same manner as above.
NMR ($CDCl_3$)
δ : 2.4 - 2.6(4H, m), 2.8 - 3.0(4H, m) 3.64(2H, s), 7.0 - 7.8(3H, m), 8.5 - 8.7(1H, m)
MS : m/z 177 (M^+)

Intermediate Example 8



To a solution of imidazole(0.68 g) and N,N-dimethylformamide (20 ml) was added 60 % sodium hydride (0.60 g)under ice-cooling, followed by stirring at room temperature for 5 minutes. To the resultant mixture was added 1-ethoxycarbonyl-4-(3-mesyloxypropyl)piperazine (3.68 g) and the mixture was stirred at room temperature overnight. To the reaction mixture were added saturated solution of sodium hydrogen carbonate (50 ml) and ethyl acetate (200 ml), the organic layer was taken using a separating funnel and dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: 10 % methanol-ethyl acetate), and dissolved in ethanol (25 ml). To the solution was added 10 % sodium hydroxide (25 ml) and the mixture was fluxed overnight. After cooling, ethyl acetate (100 ml) was added to the solution, the organic layer was separated, and the aqueous layer extracted with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 1:39 g of 1-[3-(1-imidazolyl)propyl]piperazine.
NMR ($CDCl_3$)
δ : 1.76 - 2.14(2H, m), 2.14 - 2.60(6H, m) 2.80 - 3.10(4H, m), 3.90 - 4.20(2H, m), 6.80 - 7.80(3H, m)

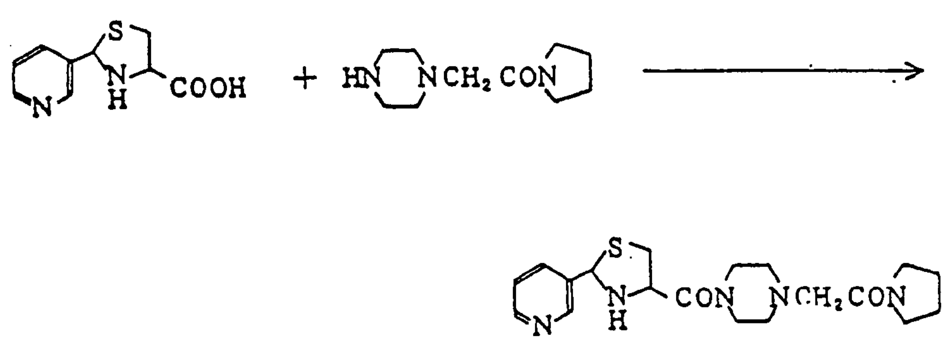
Example 1



To a solution of 2-(3-pyridyl)thiazolidine-4-carboxylic acid (2.1 g), 1-(2-pyrimidinyl)piperazine• 2 hydrochyloride (2.2 g), triethylamine (1.8 g), 1-hydroxybenzotriazole (1.5 g) and N,N-dimethylformamide (30 ml) was added dicyclohexylcarbodiimide (2.0 g) under cooling and the mixture was stirred overnight at room temperature. The resultant dicyclohexylurea was distilled off, ethyl acetate (100 ml) and water (50 ml) were added to the filtrate and the solution was basified by addition of potassium carbonate. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The organic layer and extract were combined, washed successively with water and saturated aqueous of sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethanol to give 0.8 g of 1-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]-4-(2-pyrimidinyl)piperazine.
Melting point: 156 -159 °C

Elemental analysis (for $C_{17}H_{20}N_8OS$)				
	C (%)	H (%)	N (%)	S (%)
Calc.	57.28	5.66	23.58	9.00
Found	57.52	5.70	23.37	8.87

Example 2

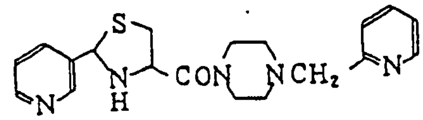


To a solution of 2-(3-pyridyl)thiazolidine-4-caroxylic acid (2.1), 1-(pyrrolidinecarbonylmethyl)piperazine-(1.8 g),1-hydroxybenzotriazole(1.5 g)and N,N-dimethylformamide (50 ml) was added dicyclohexylcarbodiimide (2 g) under ice-cooling, and the mixture was stirred overnight at room temperature. The resultant dicyclohexylurea was filtered off and the filtrate concentrated under reduced pressure. To the residue were added ethyl acetate (100 ml) and water (10 ml), the mixture was basified by addition of sodium carbonate, sodium chloride was added until saturation and the mixture was allowed to stand. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with a solution of ethyl acetate -methanol (6:4) to give 2.1 g of 1-[2-(3-pyridyl)thiazolidine-4-

ylcarbonyl]-4-[1-pyrrolidinyl)carbonylmethyl]piperazine.
NMR ($CDCl_3$)
δ : 1.6 - 2.2(4H, m), 2.5 - 2.8(4H, m), 3.8(2H, s), 2.8 - 3.8(14H, m), 3.8 - 4.3(1H, m), 5.6, 5.98(jointly 1H, s,d), 7.16 - 7.42(1H, m), 7.7 - 8.0(1H, m), 8.4 - 8.66(1H, m), 8.6 - 8.80(1H, m)
MS : m/z 389 (M^+)

Example 3

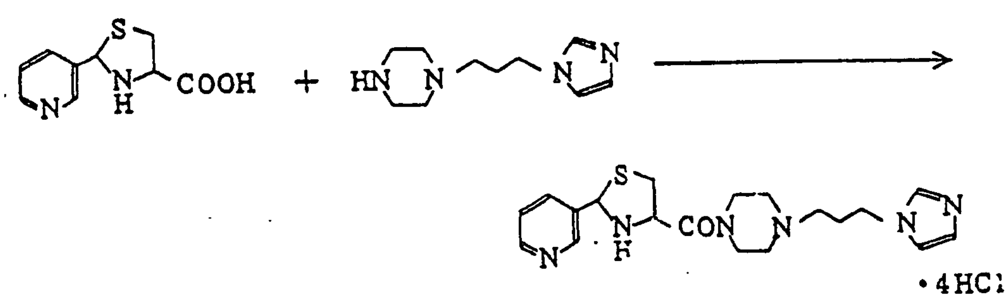
The following compound was obtained in the same manner as in Example 2.



1-[(2-pyridyl)methyl]-4-[2-(3-pyridyl)-thiazolidine-4-ylcarbonyl]piperazine

NMR ($CDCl_3$)
δ : 2.4 - 2.8(4H, m), 2.8 - 4.0(8H, m), 4.0 - 4.4(1H, m), 5.5 - 6.1(1H, m), 7.0 - 7.5(3H, m), 7.5 - 8.0(2H, m), 8.4 - 8.8(3H, m)
MS : m/z 369 (M^+)

Example 4

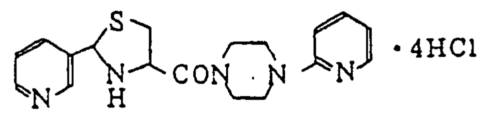


To a solution of 2-(3-pyridyl)thiazolidine-4-carboxylic acid (630 mg),1-[3-(1-imidazolyl)propyl]piperazine (580 mg), 1-hydroxybenztriazole (410 mg) and N,N-dimethylformamide (15 ml) was added dicyclohexylcarbodiimide (620 mg) under ice-cooling,and the mixture was stirred overnight at room temperature. Ethyl acetate (100 ml) was added to the solution, the resultant insoluble matter filtered off and the solution washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride in succession. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, ethyl acetate was added to the residue, the insoluble matter filtered off and the solution concentrated to dryness under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography (eluent: 20 % methanol - ethyl acetate) to give an oily product. This was dissolved in ethyl acetate (30 ml), 2 N hydrogen chloride -dioxane (4 ml) was added and the precipitated powder filtered off to give 620 mg of 1-[3-(1-imidazolyl)propyl]-4-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]piperazine• 4 hydrochloride.
Melting point: 152 - 154 °C

Elemental analysis (for $C_{19}H_{30}N_6OSCl_4 \bullet 2H_2O$)				
	C (%)	H (%)	N (%)	S (%)
Calc.	40.15	6.03	14.79	5.64
Found	40.26	5.79	14.84	5.74

Example 5

The following compound was obtained in the same manner as in Example 4.

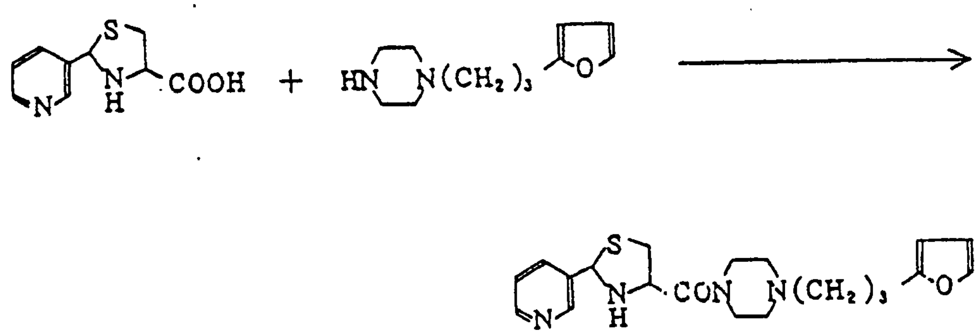


1-(2-pyridyl)-4-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]piperazine • 4 hydrochloride

Melting point: 147 - 151 °C

Elemental analysis (for $C_{18}H_{25}N_5OSCl_4 \bullet 1/2H_2O$)			
	C (%)	H (%)	N (%)
Calc.	42.37	5.14	13.72
Found	42.51	5.24	13.69

Example 6



To a solution of 2-(3-pyridyl)thiazolidine-4-carboxylic acid(0.5 g), 1-[3-(2-furyl)propyl]piperazine• 2 hydrochloride (0.54 g) and N,N-dimethylformamide (5 ml) were added N-methylmorpholine (0.2 g) and N,N-dimethylformamide (2 ml) under ice-cooling. Further 1-hydroxybenzotriazole (0.4 g) was added, then dicyclohexylcarbodiimide(0.46 g) , and the mixture was stirred overnight at room temperature. Ethyl acetate-

(50 ml)and water(10 ml)were added, the solution basified with sodium hydrogen carbonate, the insoluble matter filtered off and the solution transferred into a separtating funnel. The aqueous layer was extracted with ethyl acetate, the extract combined with the organic layer, washed with water and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with a solution of ethyl acetate - methanol (4:1) to give 0.25 g of oily 1-[3-(2-furyl)-propyl]-4-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]piperazine.

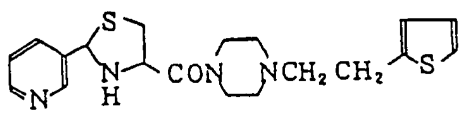
NMR ($CDCl_3$)

δ : 1.5 - 2.0(2H, m), 2.2 - 2.6(6H, m), 2.70(2H, t), 2.7 - 3.8(6H, m), 4.0 - 4.2(1H, m), 5.5 - 6.4(3H, m), 7.2 - 7.4(2H, m), 7.6 - 8.0(1H, m), 7.4 - 7.9(2H, m)

MS : m/z 386 (M^+)

Example 7

The following compound was prepared in the same manner as in Example 6.



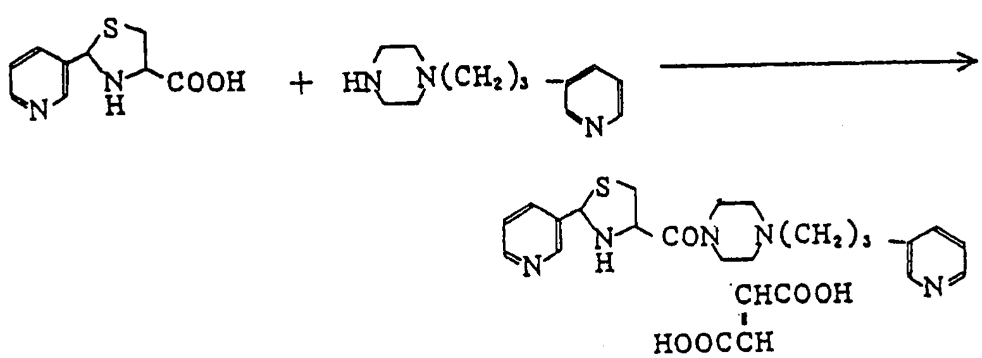
Oily 1-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]-4-[2-(2-thienyl)ethyl]piperazine.

NMR ($CDCl_3$)

δ : 2.4 - 3.8(14H, m), 3.6 - 4.3(1H, m), 5.5 - 6.1(1H, m), 6.8 - 7.0(2H, m), 7.1 - 7.4(2H, m), 7.6 - 8.0(1H, m), 8.4 - 8.9(2H, m)

MS : m/z 388 (M^+)

Example 8



To a solution of 2-(3-pyridyl)thiazolidine-4-carboxylic acid(1.7 g),1-[3-(3-pyridyl)propyl]piperazine (1.56 g),1-hydroxy-benzotriazole (1.3 g) and N,N-dimethylformamide (20 ml) was added dicyclohexylcarbodiimide(1.67 g)under ice-cooling, and the mixture was stirred overnight at room temperature. Ethyl acetate (50 ml) was added, the precipitated dicyclohexylurea filtered off, and water (30 ml) added to the filtrate; the resultant solution was basified with sodium hydrogen carbonate and transferred into a separating funnel. The aqueous layer was washed with ethyl acetate, the washings combined with the ethyl acetate layer, and the resultant ethyl acetate solution washed with water and saturated aqueous

sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography and eluted with a solution of ethyl acetate -methanol (4:1) to give 860 mg of oily 1-[3-(3-pyridyl)propyl]-4-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]-piperazine. This product was dissolved in ethanol (8ml) and after addition of fumaric acid (250 mg), the mixture allowed to stand to yield crystals. The crystals were filtered off and dried to give 580 mg of 1-[3-(3-pyridyl)propyl-4-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]piperazine• fumarate.
Melting point: 156 - 158 °C

Elemental analysis (for $C_{25}H_{31}N_5O_5S$)		
	N (%)	S (%)
Calc.	13.64	6.24
Found	13.36	6.23

Example 9

Tablet composition	
The compound obtained in Example 6	20 mg
Lactose	57 mg
Corn starch	38 mg
Hydroxypropylcellulose	4 mg
Magnesium stearate	1 mg
Total	120 mg

A homogeneous mixture is prepared from 20 g of the compound produced by Example 6, 57 g of lactose and 38 g of corn starch. Then, 40 g of 10 % hydroxypropylcellulose solution is added and the mixture is subjected to wet granulation. The granules are forced through a sieve and then dried. One gram of magnesium stearate is added to the thus-obtained granulation product. After thorough mixing the mixture is formed into tablets using a tableting machine (die-punch size: 7 m/m, 5.6 R).

Example 10

Capsule composition (per capsule)	
The compound obtained in Example 6	15 mg
Crystalline cellulose	40 mg
Crystalline lactose	144 mg
Magnesium stearate	1 mg
Total	200 mg

A homogeneous mixture is prepared from 15 g of the compound obtained in Example 6, 40 g of crystalline cellulose, 144 g of crystalline lactose and 1 g of magnesium stearate and filled into No. 3 capsules using a capsule-filling machine.

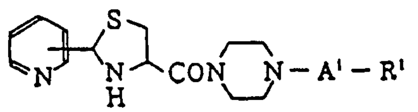
Example 11

Lyophilized preparation composition (per vial)	
The compound obtained in Example 6	1 mg
D-Mannitol	50 mg
Total	51 mg

In 800 ml of water are dissolved 1 g of the compound obtained in Example 6 and 50 g of D-mannitol in that order. Water is added to make the whole volume 1 liter. This solution is aseptically filtered, then filled in 1-ml portions into vials, and lyophilized.

Claims

1. A pyridylthiazolidine carboxamide derivative (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein A^1 is a single bond, a carbonyl group or a C_1-C_6 alkylene group which may contain a carbonyl group and R^1 is a heterocyclic group which may be substituted with a C_1-C_6 alkyl group.

2. A compound according to Claim 1 wherein R^1 is a 5- or 6-membered heterocyclic group containing one or more nitrogen atoms.

3. A compound according to Claim 2 wherein said heterocyclic group is a pyrimidinyl, pyrrolidinyl, pyridyl or imidazolyl group.

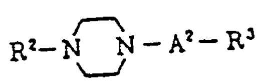
4. A compound according to Claim 1 wherein R^1 represents a 5- or 6-membered heterocyclic group containing an oxygen and/or sulfur atom.

5. A compound according to Claim 4 wherein said heterocyclic group is a furyl or thienyl group.

6. A compound according to claim 1 which is 1-[3-(2-furyl)propyl]-4-[2-(3-pyridyl)thiazolidine-4-ylcarbonyl]piperazine or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition containing a compound according to any one of Claims 1 to 6 and a pharmaceutically acceptable carrier or excipient.

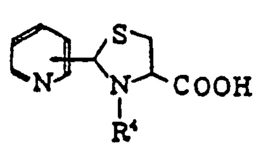
8. An N-substituted piperazine derivative (II) or a salt thereof :



(II)

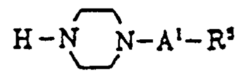
wherein A^2 is a C_1-C_6 alkylene group which may contain a carbonyl group; R^2 is a hydrogen atom or an amino-protecting group and R^3 is a heterocyclic group (except a pyridyl group) which may be substituted with a C_1-C_6 alkyl group.

9. A process for preparing a compound according to Claim 1 which comprises
(a) reacting thiazolidine carboxylic acid (III) or reactive derivative thereof



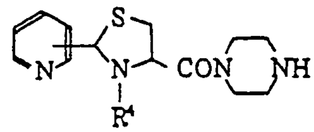
(III)

with 4-substituted piperazine (IV) or salt thereof



(IV) ,

or (b) reacting piperazinamide compound (V) :

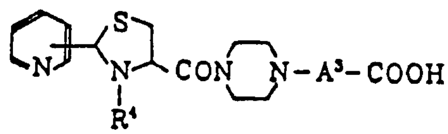


(V)

with carboxylic acid (VI) or reactive derivative thereof

R^5-A^3-COOH (VI),

or (c) reacting carboxylic acid (VII) or reactive derivative thereof

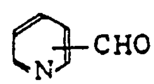


(VII)

with cyclic amine (VIII)

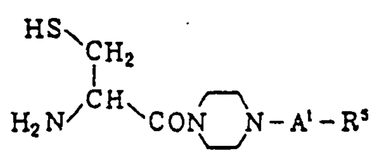
(VIII) ,

or (d) reacting carbonyl compound (IX)



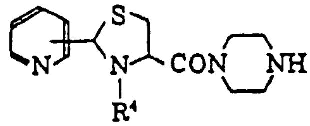
(IX)

with β-mercaptoamine (X)



(X) ,

or (e) reacting compound (XI)

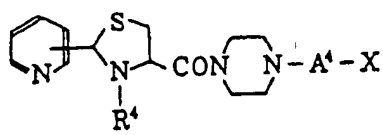


(XI)

with compound (XII)

R^5-A^4-X (XII) ,

or (f) reacting compound (XIII)



(XIII)

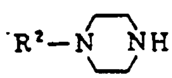
with compound (XIV)

(XIV) ,

and in each of (a) to (f) optionally removing any protective group, and/or optionally converting the product to or from salt form, wherein A^1 and R^1 are as defined in Claim 1, R^4 is a hydrogen atom or an amino-protecting group, R^5 is R^1 which may have an amino-protecting group, A^3 is a single bond or a C_1-C_5 alkylene group,

is a heterocyclic group with one or more non-tertiary ring nitrogen atoms, X is a halogen atom or an organic sulfonic acid residue, and A^4 is an A^1 group where the X-end is not a carbonyl group.

10. A process for preparing an N-substituted piperazine derivative according to Claim 8 which comprises (a) reacting piperazine compound (XV)



(XV)

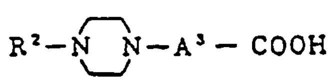
with halide or sulfonate compound (XVI)

R^6-A^4-X (XVI) ,

or (b) reacting compound (XV) with carboxylic acid (XVII) or reactive derivative thereof

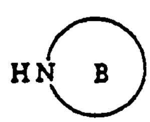
R^6-A^3-COOH (XVII),

or (c) reacting compound (XVIII) or reactive derivative thereof



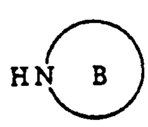
(XVIII)

with compound (XIV)



(XIV) ,

and in each of (a) to (c) optionally removing any protective group and/or converting the product to or from salt form, wherein R^2 and R^3 are as defined in Claim 8, A^3, A^4,



and X are as defined in Claim 9, and R^6 is an R^3 group which may have an amino-protective group.